

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 9/48, 9/20	A1	(11) International Publication Number: WO 92/04013 (43) International Publication Date: 19 March 1992 (19.03.92)
(21) International Application Number: PCT/EP91/01562 (22) International Filing Date: 15 August 1991 (15.08.91) (30) Priority data: 21338A/90 30 August 1990 (30.08.90) IT (71) Applicant (for all designated States except US): EURAND INTERNATIONAL SPA [IT/IT]; Via M de Vizzi, 60, I-20092 Cinisello Balsamo (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): BONGIOVANNI, Giovanni [IT/IT]; Via F Brunelleschi, 9, I-20046 Biassono (IT). CALANCHI, Massimo, Maria [IT/IT]; Via Catalafimi, 12, I-20052 Monza (IT). MARCONI, Marco, Giuseppe, Raffaele [IT/IT]; Via Aurora, 6, I-20092 Cinisello Balsamo (IT).		(74) Agents: PORTER, G., R. et al.; Wyeth Laboratories, Huntercombe Lane South, Taplow, Nr Maidenhead, Berkshire SL6 0PH (GB). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), SU*, US. Published <i>With international search report.</i>
(54) Title: MULTIPARTICULATE SUSTAINED RELEASE MATRIX SYSTEM (57) Abstract The present invention relates to an oral dosage system of pharmacologically active substances consisting of different small tablets, each having a prolonged and controlled release, filled into hard gelatin capsules. Specifically the small tablets have a hydrophilic matrix made of xanthan gum, alone or mixed with other hydrophilic polymers, by which the slow release of the drug along the gastro-intestinal tract is obtained.		

+ DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU ⁺	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TC	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

MULTIPARTICULATE SUSTAINED RELEASE MATRIX SYSTEM

The present invention relates to an oral dosage system of pharmacologically active substances consisting of different small tablets, each having a prolonged and controlled release, filled into hard gelatin capsules.

- 5 Hydrophilic matrix tablets consist fundamentally of a homogeneous mixture of the active medicament and one or more polymers which dissolve slowly in water.

For Example:

- 10 US Patent No. 4,259,341 to Lowey, US Patent No. 3,870,790 to Lowey et al and US Patent No. 4,226,849 to Schor and US Patent No 4,357,469 to Schor concern the preparation of tablets with a hydrophilic matrix of hydroxypropylmethylcellulose, alone or mixed with other cellulose derivatives, which have undergone treatments, 15 that is forced dehydration, humidification, hydrolysis and oxidation.

- 20 US Patent No. 4,369,172 and No. 4,389,393 to Schor et al which concern the use of one or more types and well-defined quantities of hydroxypropylcellulose alone or mixed with methylcellulose and/or sodium carboxymethylcellulose.

- 25 US Patent No. 4,167,448 and No. 4,126,672 to Sheth et al which concern the use of hydroxypropylmethylcellulose for the preparation of tablets and especially hydrophilic matrix capsules in such a form that they float in the digestive juices of the stomach.

- 2 -

5 The article entitled "A Review of Cellulose Ethers in
Hydrophylic Matrices for Oral Controlled-release Dosage
Forms" by D.A. Alderman, published in Int.J.Pharm.Tech
and Prod.Mfr., 5 (3) 1-9, 1984, describes extensively
the use of hydroxypropylmethylcellulose to prepare
controlled-release hydrophilic matrix and examines the
influence of various parameters characteristic of
hydroxypropylmethylcellulose, such as molecular weight,
degree of substitution; granulometric distribution,
10 hydration velocity, on the release of the active
medicament.

The EURO PCT Patent Application EP 261,213 (WO 87/5212)
(corresponding to Italian Patent application No. 19 675
A/86) discloses hydrophilic matrix tablets in which the
15 matrix consists of Xanthan Gum alone or in a mixture
(50% maximum) with hydrophilic cellulose polymers such
as hydroxypropylmethylcellulose and
hydroxypropylcellulose.

20 The advantage of these large matrix polymers is their
low cost, but they have various disadvantages since
they tend to adhere to the stomach and intestinal
walls, causing irritation of the mucosa and irregular
absorption of the active medicament.

25 These disadvantages are overcome by the
multiparticulate form as spherules composed of active
medicament coated with a polymeric membrane which
delays the dissolution. These spherules of
controlled-release medicament are filled into hard
gelatin capsules which, when ingested, dissolve to
30 release the tens and sometimes hundreds of spherules
which disperse along the gastro-intestinal tract, thus

- 3 -

avoiding a high local concentration of the active medicament.

5 With this multiparticulate form the following advantages are obtained: a more reproducible release; an improved gastro-intestinal tolerance; a more uniform concentration of the active medicament in the blood without "peaks", which often cause negative side effects, and therefore a greater acceptability for the patient. However, the methods of producing the small
10 sustained-release spheres are very long and complex and therefore expensive. In addition the dimensions of the spherules are not equal, but since they are distributed in a large range the release of single spherules, after coating with the delaying membrane, will not be
15 homogeneous either.

These disadvantages can be overcome by preparing the tablets with a matrix of small dimensions (also called minitablets) to fill hard gelatin capsules, so obtaining a multiparticulate form.

20 The production of small hydrophilic matrix tablets however is not very easy and presents two main problems. The first is due to the fact that the small dimensions, the permeability and the solubility of the polymers utilized for the hydrophilic matrix
25 preparation do not permit to delay sufficiently the dissolution of the active medicament.

The second is due to the fact that the minitablets form gelatinous layer and stick together on contact with the gastro-intestinal juices. In fact when the gelatin
30 capsule is ingested and dissolves, the polymer

- 4 -

constituent of the minitabiet matrix hydrates and forms a gelatinous layer. The single units stick together giving rise to a single mass which proceeds along the gastro-intestinal tract like a single large tablet so cancelling out the desired advantages of the multiparticulate form.

G.B. Patent No 2,176,999 managed to get around the first of these problems by the addition of an ionic substance to the minitabiet formulation, in addition to the hydroxylalkylcellulose ethers, with a large opposite to that of the active medicament, preferably an ionic exchange resin, with the function of delaying the release of the active medicament as specified in the text of the patent and as known (see for example European Patent Appln. 0294103 A of Muneo Nonomura et al)..

The object of the present invention are small hydrophilic matrix tablets which are not only slow-releasing but also do not aggregate when hydrated.

In fact we have discovered, very surprisingly, that if natural xanthan gum is used as the hydrophilic matrix, minitabiet with the above-mentioned characteristics are obtained.

Once put in the capsule, these minitabs permit the administration of an economical controlled-release multiparticulate form and the units remain in single entities along the gastro-intestinal tract.

According to the invention there is provided a

- 5 -

pharmaceutical dosage form comprising a hard gelatin capsule containing a multiplicity of minitables providing prolonged and regular release of the active ingredient, said tablets comprising one or more active medicaments contained within a matrix which provides a sustained release effect, the matrix consisting essentially of xanthan gum or a mixture of xanthan gum and one or more natural or synthetic polymers, which hydrate and dissolve in water or gastric juices.

The present invention concerns the preparation of controlled-release minitables obtained by compression of an active medicament, xanthan gum and possible other inert excipients commonly utilized for the production of tablets such as lubricants, fillers and flowing agents.

We have found, very surprisingly, that if xanthan gum is used as a hydrophilic matrix, the release of the active medicament is slowed down. Moreover when the polymer is hydrated giving rise to the formation of a superficial gelatinous layer the single units do not stick together therefore maintaining all the advantages of multiparticulate form.

The xanthan gum is a natural polymer with a high molecular weight or more specifically a biopolysaccharide, fermentation product of the microorganism *Xanthomonas campestris*. The structure, the molecular weight, and the dissolution properties of this polymer are constant and reproducible in strictly controlled working conditions.

Xanthan gum is used in numerous fields including the pharmaceutical, cosmetic and food industries. In these

- 6 -

cases the thickening and stabilizing properties of emulsions or suspensions given by xanthan gum in solution are made use of.

5 With the present invention we found that it is possible to make use of xanthan gum's properties also in solid forms of medicament, using it for the preparation of the hydrophilic matrix in which xanthan gum has a retarding effect on the dissolution of the medicament.

10 The matrix can consist of xanthan gum only or as a mixture of xanthan gum always being 50% or higher with respect to the polymer.

The delaying matrix is mixed in suitable apparatus with the desired active medicament or even medicaments to be administered in a sustained-release formulation. Among
15 the active medicaments we cite as an illustrative, but not restrictive, example adrenergicamines (ethylephrine, phenylephrine, phenylpropanolamine, d-pseudoephendrin), antispasmodics (scopolamine, and other alkaloids of belladonna, papaverine and
20 derivatives), antihistamines (broncopheniramine, chlorpheniramine, diphenylpiraline, dimenhydr(in)ate), anorexics (norpsuedoephedrin, fentermine, diethylpropion, flenfuramine), antiasthmatics (theophylline, salbutamol, terbutaline), antianginous
25 (isosorbide-5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, nitroglycerin, nifedipin, diltiazem), anti-inflammatory and antipyretics (indomethacin, ibuprofen, ketoprofen, aspirin, paracetamol, phenacetin), antihypertensives
30 (nifedipin, idralazin, prazosin, verapamil), antidepressives (amitriptyline, lithium salts),

- 7 -

5 antitussive (destromethorphan, noscapine, codeine),
gastroenteric (cimetidine, ranitidine, metoclopramide)
antiarrhythmic (procainamide, lidocaine, flecainide,
propafenone), analgesics (morphine), vitamins (ascorbic
acid) and their salts used in the pharmaceutical field.

Apart from polymers and medicaments, inert excipients
commonly used by experts in the art may be present in
the formulation, in order to improve its
characteristics.

10 For example in the preparation of minitablets,
lubricants, inert excipients, etc. can be added to
improve the flowability of the powder, the appearance,
the precision of the dose.

15 The quantity of matrix used to delay the release of the
active medicament can vary widely depending on whether
the formulation consists only of active medicament and
matrix or if there are other excipients present, in
various quantities according to whether the active
medicament is very or not very soluble and whether the
20 dose is high or low.

The minitablets are produced using the usual tableting
machines as for example the Ronchi rotary type AM13
equipped with punches and matrices adapted in order to
obtain minitablets with a diameter less than 4 mm and
preferably between 2 - 2.5 mm.
25

The invention also includes a method for the
preparation of a pharmaceutical dosage form which
method comprises mixing an active medicament with
xanthan gum or a mixture of xanthan gum and one or more

- 8 -

5 natural or synthetic polymers, which hydrate and dissolve in water or gastro-intestinal juices, forming the mixture into minitabets, filling the minitabets into hard gelatin capsules so that each capsule contains a multiplicity of minitabets, the xanthan gum or xanthan gum mixture providing a matrix from which in use the active medicament has a prolonged and regular release.

10 The following examples which serve to better illustrate the invention must not be considered in any way as restrictive of the scope of the present invention and possible variations are obvious for experts in this field.

EXAMPLE 1

15 A) Preparation of the Mixture

Transfer the following raw materials, previously sieved through a 0.5 mm sieve, in a stainless steel laboratory cube mixer

20	ibuprofen	219.0g
	xanthan gum	45.0g
	cornstarch	12.0g
	glyceryl behenate	4.5g
	magnesium stearate	4.5g

mix for about 15 minutes.

25 B) Preparation of the Minitabets

The mixture obtained from A) is compressed with a tabletting machine, model Ronchi AM13 equipped with

- 9 -

punchers (diameter 2 mm, bending radius 3 mm) giving minitablets with an average weight of 9.2 mg and each containing 6 mg of ibuprofen.

C) Preparation of the Final Pharmaceutical Form

5 Utilizing hard gelatin capsules, type Coni Snap Supro-A, 34 of the small tablets produced in B were introduced into each capsule with a suitable capsule filling machine.

Each capsule contains 200 mg of ibuprofen.

10 D) Analysis

The minitablets were analysed with the rotating paddle method described in the current edition of the US Pharmacopoeia (USP) using 900 ml of artificial intestinal juice with pH 6.8 and a rotation speed of 50 rpm.

% Release

20 -after 1 hour: 27.0
 -after 2 hours: 44.4
 -after 3 hours: 59.7
 -after 4 hours: 73.0
 -after 5 hours: 85.1
 -after 6 hours: 94.5

EXAMPLE 2

A) Preparation of the mixture

- 10 -

Transfer 2550 g of sodium diclofenac into a laboratory blender and blend with 570 g of a solution of 15% hydroxypropylcellulose in 95% alcohol.

5 Granulate the paste obtained through a 1200 μ m mesh screen and subsequently through 800 μ m and 700 μ m mesh screens.

The granules are dried at about 40° C for 12-15 hours in a circulating air oven and selected between 300 and 700 μ m.

10 The following materials are transferred in a double cone shaped laboratory mixer:

granulated sodium diclofenac (300-700 μ m)	800.0g
xanthan gum	1140.0g
silicon dioxide	20.0g
15 magnesium stearate	40.0g

mix for about 15 minutes.

B) Preparation of the Minitablets

20 The mixture obtained from A) is compressed with a tabletting machine, model Ronchi AM13 equipped with punchers (diameter 2mm, bending radius 3mm) giving minitables with an average weight of 7.7 mg and each containing 2.9 mg of diclofenac.

C) Preparation of the Final Pharmaceutical Form

25 Utilizing hard gelatin capsules, type Snap Fit size 1,35 of the small tablets produced in B were introduced into each capsule with a suitable capsule filling machine.

- 11 -

Each capsule contains 100 mg of sodium diclofenac.

D) Analysis

5 The minitablets were analysed with the rotating paddle method described in the current edition of the US Pharmacopoeia (USP) using 900 ml of artificial intestinal juice with pH 6.8 and a rotation speed of 50 rpm.

% Release

10 -after 1 hour: 30.2
 -after 2 hours: 52.9
 -after 3 hours: 65.1
 -after 4 hours: 72.6
 -after 6 hours: 99.0

EXAMPLE 3

15 A) Preparation of the Mixture

Transfer the following raw materials, previously sieved through a 0.5 mm sieve, in a stainless steel laboratory cube mixer

20 granulate theophylline (200-400 µm) 108.7g
 xanthar. gum 41.5g
 hydroxypropylmethylcellulose 44.5g
 silicone dioxide 0.9g
 magnesium stearate 1.4g
 Mix for about 15 minutes

25 B) Preparation of the Minitablets

- 12 -

5 The mixture obtained from A) is compressed with a compressing machine, model Ronchi AM13 equipped with punchers (diameter 2 mm, bending radius 3 mm) giving minitabs with an average weight of 8.1 mg and each containing 4.4 mg of theophylline.

C) Preparation of the Final Pharmaceutical Form

10 Utilizing hard gelatin capsules, type Coni Snap Fit size 0,45 of the small tablets produced in B were introduced into each capsule with a suitable filling machine.

Each capsule contains 200 mg of theophylline.

D) Analysis

15 The minitabets were analyzed with the rotating paddle method described in the current edition of the US Pharmacopoeia (USP) using 900 ml of artificial intestinal juice with pH 7.5 and a rotation speed of 50 rpm.

% Release

20 -after 1 hour: 43.5
 -after 2 hours: 68.9
 -after 3 hours: 99.0

The minitabets were analyzed as described above using 900ml of artificial gastric juice with pH 1.2

% Release

25 -after 1 hour: 53.9
 -after 2 hours: 77.7
 -after 4 hours: 100

- 13 -

CLAIMS

1. A pharmaceutical dosage form comprising a hard gelatin capsule containing a multiplicity of minitabets providing prolonged and regular release of the active ingredient, said tablets comprising one or more active medicaments contained within a matrix which provides a sustained release effect, the matrix consisting essentially of xanthan gum or a mixture of xanthan gum and one or more natural or synthetic polymers, which hydrate and dissolve in water or gastric juices.
2. A pharmaceutical dosage form as claimed in Claim 1, wherein the matrix comprises at least 50% of xanthan gum.
3. A pharmaceutical dosage form as claimed in Claim 1 or Claim 2, wherein the matrix consists essentially of xanthan gum and one or both of hydroxypropylcellulose or hydroxypropylmethylcellulose .
4. A pharmaceutical dosage form as claimed in any one of the preceding Claims wherein the minitabets also contain conventional inert excipients.
5. A pharmaceutical dosage form as claimed in any one of the preceding claims wherein the active medicament is ibuprofen, theophylline or sodium diclofenac .
6. A pharmaceutical dosage form as claimed in any one of the preceding Claims wherein the capsule contains from 30 - 50 minitabets.
7. A method for the preparation of a pharmaceutical

- 14 -

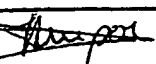
dosage form which method comprises mixing an active medicament with xanthan gum or a mixture of xanthan gum and one or more natural or synthetic polymers, which hydrate and dissolve in water or gastro-intestinal juices, forming the mixture into minitables, filling the minitables into hard gelatin capsules so that each capsule contains a multiplicity of minitables, the xanthan gum or xanthan gum mixture providing a matrix from which in use the active medicament has a prolonged and regular release.

8. A method as claimed in Claim 7, wherein the dosage form is as claimed in any one of Claims 1 - 6.

9. A pharmaceutical dosage form as claimed in Claim 1, substantially as hereinbefore described in any one of Examples 1 - 3.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01562

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 9/48 A 61 K 9/20		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.C1.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	GB,A,2176999 (THE UNIVERSITY OF NOTTINGHAM) 14 January 1987, see claims 1,7-9; page 1, lines 58-108; page 2, lines 41-45; page 3, lines 32-37 (cited in the application)	1,3,4,6 -9
Y	---	2,5
Y	EP,A,0234670 (THE BOOTS CO. PLC) 2 September 1987, see claims 1-3,7,9,15; page 15; example 1 -----	2,5
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
17-10-1991		19 NOV 1991
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		 Mme N. KUIPER

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9101562
SA 50208

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/11/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 2176999	14-01-87	None	
EP-A- 0234670	02-09-87	AU-B- 608208	28-03-91
		AU-A- 6762587	23-07-87
		JP-A- 62181227	08-08-87